Supplemental Table Trials Investigating Renal Outcomes with SGLT2 Inhibitors

Title (acronym)*	SGLT2 inhibitor	Study type (planned or *actual* enrollment)	Estimated completion date	NCT identifier	Trial objectives
Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE)	Canagliflozin	RCT Phase 3 (N = 4,401)	Completed[27] End point met, terminated early (June 2018)†	NCT02065791	Evaluate whether canagliflozin has a renal and CV protective effect in reducing the progression of renal impairment relative to placebo in patients with T2DM and Stage 2 or 3 CKD and macroalbuminuria, who are receiving standard of care including a maximum tolerated labeled daily ACEI or ARB
Efficacy and Safety of Canagliflozin (TA-7284) in Patients With Diabetic Nephropathy	Canagliflozin	RCT Phase 3 (N = 300)	September 2021	NCT03436693	Assess the effect of canagliflozin on renal outcomes in Japanese patients with T2DM, proteinuria, and eGFR $\geq$30 to $<$90 mL/min/1.73 m^2 over 2 years
An Open Label, Phase IV, Mechanistic, 3-Arm Study to Evaluate the Natriuretic Effect of 2-Week Dapagliflozin Treatment in T2DM Patients With Either Preserved or Impaired Renal Function and Non-diabetics With Impaired Renal Function (DAPASALT)	Dapagliflozin	Open label Phase 4 (N = 51)	December 2019	NCT03152084	Determine the effects of dapagliflozin on changes in 24-hour sodium excretion, 24-hour SBP, plasma volume, ECF volume, and UACR, and to evaluate pharmacokinetics in the following groups of subjects: (1) T2DM and CKD (eGFR $\geq$25 and $\leq$50 mL/min/1.73 m^2), (2) T2DM and normal renal function, or (3) CKD (eGFR $\geq$25 and $\leq$50 mL/min/1.73 m^2) and no T2DM
A Study to Assess the Renoprotective Effects of the SGLT2 Inhibitor Dapagliflozin in Non-diabetic Patients With Proteinuria: A Randomized Double Blind 6-Weeks Cross-over Trial (DIAMOND)	Dapagliflozin	Crossover trial Phase 2 (N = 50)	December 2019	NCT03190694	Examine effects of dapagliflozin on proteinuria and renal hemodynamics in nondiabetic subjects with eGFR $\geq$25 mL/min/1.73 m^2 and 500−3,500 mg/g proteinuria on RAAS blockade. Outcome measures include change in 24-hour protein excretion, GFR (iohexol), BP, body weight, neurohormones, or biomarkers
Acute Kidney Injury in Patients on Dapagliflozin and Other Antidiabetic Medications	Dapagliflozin	Observational, retrospective cohort (N = 91,927)	November 2019	NCT02695082	Evaluate the incidence of hospitalization for acute kidney injury among patients with T2DM who are new users of dapagliflozin compared with new users of other diabetes agents in a class *other than* SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy based on data from 3 administrative health care data sources in the US and UK

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Supplemental Table (*Continued*)

Title (acronym)*	SGLT2 inhibitor	Study type (planned or *actual* enrollment)	Estimated completion date	NCT identifier	Trial objectives
A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD)	Dapagliflozin	RCT Phase 3 (N = 4,000)	November 2020	NCT03036150	Evaluate the effect of dapagliflozin added to standard of care on renal and CV outcomes in subjects with eGFR 25—75 mL/min/1.73 m^2 and proteinuria
Empagliflozin in Renal Transplant Recipients (EMPA-RenalTx)	Empagliflozin	RCT Phase 4 (N = 49)	Completed	NCT03157414	Examine the effects of 24 weeks of empagliflozin in subjects with kidney transplant (eGFR $\geq$30 mL/min/1.73 m^2) and post-transplant T2DM. Measures include various indices of glycemic control, including weighted glucose control by continuous monitoring, body weight, waist-hip ratio, bone mineral density (DEXA), BP, pulse wave velocity (Sphygmacor), and eGFR (cystatin C)
Empagliflozin and Renal Oxygenation in Healthy Volunteers (EMPA-REIN)	Empagliflozin	RCT Phase 2 (N = 45)	December 2018	NCT03093103	Measure the effects of empagliflozin (4 weeks) on renal oxygenation (BOLD MRI), resistive indices (ultrasound), 24-hour ABP, and diurnal variations in electrolyte and lithium clearance in subjects without T2DM stratified by BMI
Empagliflozin and RAS in Kidney Disease (EMPRA)	Empagliflozin	RCT Phase 2 (N = 48)	August 2019	NCT03078101	Examine how adding empagliflozin to ACEI for 12 weeks affects several endpoints (e.g., Ang 1—7, Ang II, HDL-C composition, albuminuria, eGFR, BP, urinary glucose and electrolytes, urinary RAS metabolites, body fluid (bioimpedance), oxygen consumption by PBMCs) in patients with CKD with or without T2DM
SGLT2 Inhibition in Combination With Diuretics in Heart Failure (RECEDE-CHF)	Empagliflozin	Crossover RCT Phase 4 (*N = 23*)	Completed	NCT03226457	Examine the effects of empagliflozin in subjects with T2DM and mild HFrEF on loop diuretic. Outcomes include urine flow rate after acute water load or bolus furosemide, eGFR, and albuminuria
Post-authorization Safety Study in Patients With T2DM to Assess the Risk of Liver Injury, Kidney Injury, Urinary Tract and Genital Infections, and Diabetic Ketoacidosis in Patients Treated With Empagliflozin, Compared to DPP-4 Inhibitors	Empagliflozin	Retrospective, observational cohort study (N = 14,800)	January 2020	NCT02864914	Evaluate the liver and renal safety of empagliflozin relative to DPP-4 inhibitors in the postmarketing setting among adult patients with T2DM and at least 12 months of continuous enrollment in specific databases

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Supplemental Table (*Continued*)

Title (acronym)*	SGLT2 inhibitor	Study type (planned or *actual* enrollment)	Estimated completion date	NCT identifier	Trial objectives
Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects (SUGAR-DM-HF)	Empagliflozin	RCT Phase 4 (N = 130)	February 2020	NCT03485092	Evaluate the effect of empagliflozin on CVD outcomes in subjects with T2DM and HFrEF over 30 weeks. Outcome measures include LV end systolic volume, LV strain, LV microvascular perfusion, ECV fraction, QoL, exercise capacity (6MWT), eGFR; most measures are by cardiac MRI
Effects of Empagliflozin on Endogenous Glucose Production in ESRD	Empagliflozin	Crossover RCT Phase 2 (N = 25)	December 2020	NCT03713190	Examine the acute impact of SGLT2 inhibition on endogenous glucose production and plasma glucagon levels in patients with ESRD. Secondary endpoints include the mean difference in plasma glucose, insulin, C-peptide, FFA, epinephrine, norepinephrine, cortisol, and BP during the last hour of the experiment between empagliflozin vs placebo administration in patients
Renal Actions of Combined Empagliflozin and Linagliptin in Type 2 Diabetes (RACELINES)	Empagliflozin (and linagliptin)	RCT Phase 4 (N = 66)	December 2020	NCT03433248	Evaluate the interactions between an SGLT2 inhibitor and DPP-4 inhibitor (empagliflozin and linagliptin will be added sequentially in random order in 8-week blocks) in subjects with T2DM. Outcome measures include changes in GFR (inulin clearance) in fasting and postprandial states, 24-hour urine chemistries, UACR, heart rate, BP, anthropometrics, systemic hemodynamics and microvascular function (NexFin), insulin sensitivity, beta-cell function, DPP-4 activity, and ACE activity, at different time points
The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY)	Empagliflozin	RCT Phase 3 (N = 5,000)	June 2022	NCT03594110	Assess impact of empagliflozin on renal and CV outcomes on top of standard of care in subjects with or without diabetes and with CKD (eGFR $\geq$20 to $<$45 mL/min/1.73 m^2 or $\geq$45 to $<$ 90 mL/min/1.73 m^2 with proteinuria). The composite primary outcome consists of time to first occurrence of (1) kidney disease progression (defined as ESRD, a

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Title (acronym)*	SGLT2 inhibitor	Study type (planned or *actual* enrollment)	Estimated completion date	NCT identifier	Trial objectives
					sustained decline in eGFR to <10 mL/min/1.73 m^2, renal death, or a sustained decline of $\geq 40\%$ in eGFR from randomization); or (2) CV death
Empagliflozin in Heart Failure: Diuretic and Cardio-Renal Effects	Empagliflozin	Crossover RCT Phase 2 (N = 21)	Completed	NCT03027960	To prove the existence of, and probe the mechanisms underlying, cardio-renal effects of empagliflozin in patients with T2DM, stable HF, and eGFR >45 mL/min/1.73 m^2 to determine whether acute SGLT2 inhibition augments the natriuretic effect of a loop diuretic
Empagliflozin in Early Diabetic Kidney Disease	Empagliflozin	RCT Phase 3 (N = 300)	August 2024	NCT03173963	Examine the effects of empagliflozin on structural and functional kidney disease progression in American Indians with T2DM and early diabetic kidney disease over the 3-year study period. Outcome measures include a change in cortical interstitial fractional volume assessed by kidney biopsy specimens, GFR, renal plasma flow, fibrosis detected by MRI, and renal gene expression and epigenetic profiling
Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With T2DM and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED)	Sotagliflozin	RCT Phase 3 (N = 10,500)	March 2022	NCT03315143	Demonstrate that when compared with placebo, sotagliflozin does not increase the risk of MACE (CV death, nonfatal MI, or nonfatal stroke) and reduces risk of CV death or HHF in patients with T2DM, CV risk factors, and moderately impaired renal function

6MWT = 6-minute walk test; ABP = ambulatory blood pressure; ACE = angiotensin-converting enzyme; ACEI = ACE inhibitor; Ang 1–7 = angiotensin 1–7; Ang II = angiotensin II; ARB = angiotensin receptor blocker; BMI = body mass index; BOLD = blood oxygenation level dependent; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = CV disease; DEXA = dual-energy X-ray absorptiometry; DPP-4 = dipeptidyl peptidase-4; ECF = extracellular fluid; ECV = extracellular volume; eGFR = estimated GFR; ESRD = end-stage renal disease; FFA = free fatty acid; GFR = glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; HFrEF = HF with reduced ejection fraction; HHF = hospitalization for HF; LV = left ventricular; MACE = major adverse CV event; MI = myocardial infarction; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; QoL = quality of life; RAAS = renin-angiotensin-aldosterone system; RAS = renin-angiotensin system; RCT = randomized controlled trial; SBP = systolic blood pressure; SCr = serum creatinine; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus; UACR = urine albumin-to-creatinine ratio.

*Not all trials have acronyms.

†Achieved the prespecified goal of reducing the combined incidence of ESRD, doubling of SCr, and renal or CV death.